Complete Summary

GUIDELINE TITLE

Valproic acid poisoning: an evidence-based consensus guideline for out-of-hospital management.

BIBLIOGRAPHIC SOURCE(S)

Manoguerra AS, Erdman AR, Woolf AD, Chyka PA, Caravati EM, Scharman EJ, Booze LL, Christianson G, Nelson LS, Cobaugh DJ, Troutman WG. Valproic acid poisoning: an evidence-based consensus guideline for out-of hospital management. Washington (DC): American Association of Poison Control Centers; 2006. 23 p. [85 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Valproic acid poisoning

Note:

- This guideline applies to the acute ingestion and acute-on-chronic ingestion of immediate-release and extended-release dosage forms of valproic acid, divalproex, and valproate sodium alone. Co-ingestion of additional substances could require different referral and management recommendations depending on the combined toxicities of the substances.

- This review focuses on the ingestion of more than a single therapeutic dose and the effects of an overdose. Although therapeutic doses of valproic acid can cause adverse effects in adults and children, some idiosyncratic and some dose-dependent, these cases are not considered.

GUIDELINE CATEGORY

Evaluation
Management
Risk Assessment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Internal Medicine
Obstetrics and Gynecology
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Emergency Medical Technicians/Paramedics
Nurses
Pharmacists
Physicians

GUIDELINE OBJECTIVE(S)

To assist poison center personnel in the appropriate out-of-hospital triage and initial out-of-hospital management of patients with a suspected ingestion of valproic acid by:

- Describing the process by which an ingestion of valproic acid might be managed
- Identifying the key decision elements in managing cases of valproic acid ingestion
- Providing clear and practical recommendations that reflect the current state of knowledge
- Identifying needs for research

TARGET POPULATION

Children and adults (including pregnant women) with suspected valproic acid poisoning

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Assessment of key decision elements for triage
    - Patient intent
    - Dose and formulation
    - Presence of symptoms
    - Time of ingestion

Management

1. Referral to an emergency department
2. Activated charcoal administration by health professionals
3. Evaluation of pregnant women by their obstetrician
4. Naloxone
5. Benzodiazepines administered by emergency medical services (EMS) personnel
6. Home observation

Note: The following measure was considered but not recommended: induction of emesis.

MAJOR OUTCOMES CONSIDERED

- Signs and symptoms of toxicity
- Mortality
- Toxic dose

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Search Strategy

Literature searches for relevant articles were performed by a single investigator. The National Library of Medicine's PubMed database was searched (through March 2006) using valproic acid as a Medical Subject Headings (MeSH) term with the subheadings poisoning or toxicity, limited to humans. The PubMed database was further searched using valproic acid, valproate, and divalproex as textwords (title, abstract, MeSH term, CAS registry) plus either poison* or overdos* or intox* or toxic*, limited to humans. This process was repeated in International Pharmaceutical Abstracts (1970–March 2006, excluding abstracts of meeting presentations), Science Citation Index (1977–March 2006), Database of Abstracts of Reviews of Effects (accessed March 2006), Cochrane Database of Systematic Reviews (accessed March 2006), and Cochrane Central Register of Controlled Trials (accessed March 2006). Reactions (1980–March 2006), the valproic acid poisoning management in Poisindex, and the bibliographies of recovered articles were reviewed to identify previously undiscovered articles. Furthermore, North

American Congress of Clinical Toxicology (NACCT) abstracts published in the Journal of Toxicology Clinical Toxicology (1995–2004) and Clinical Toxicology (2005) were reviewed for original human data.

Six major toxicology textbooks were reviewed for recommendations on the management of valproic acid poisonings and for citations of additional articles with original human data in the chapter bibliographies. The Toxic Exposure Surveillance System (TESS) maintained by the American Association of Poison Control Centers was searched for deaths resulting from valproic acid poisoning. These cases were abstracted for review by panel members. All United States poison control centers were surveyed in 2006 to ascertain their out-of-hospital management and triage practices for valproic acid poisonings.

Criteria Used to Identify Applicable Studies

The recovered citations were entered into an EndNote library and duplicate entries were eliminated. The abstracts of these articles were reviewed, searching specifically for those that dealt with estimations of doses with or without subsequent signs or symptoms of toxicity and management techniques that might be suitable for out-of-hospital use (e.g., gastrointestinal decontamination). Articles that did not meet either of the preceding criteria, did not add new data (e.g., reviews, editorials), or that exclusively described inpatient-only procedures (e.g., dialysis) were excluded.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Level of Evidence	Description of Study Design
1a	Systematic review (with homogeneity) of randomized clinical trials
1b	Individual randomized clinical trials (with narrow confidence interval)
1c	All or none (all patients died before the drug became available, but some now survive on it; or when some patients died before the drug became available, but none now die on it.)
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality randomized clinical trial)
2c	"Outcomes" research
3a	Systemic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case series, single case reports (and poor quality cohort and case

Level of Evidence	Description of Study Design
	control studies)
5	Expert opinion without explicit critical appraisal or based on physiology or bench research
6	Abstracts

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Data Extraction Process

All articles that were retrieved from the original search were reviewed by a single trained physician abstractor. The complete paper was reviewed for original human data regarding the toxic effects of valproic acid or original human data directly relevant to the out-of-hospital management of patients with valproic acid toxicity or overdose. Relevant data (e.g., dose, effects, time of onset of effects, therapeutic interventions or decontamination measures provided, efficacy or results of any interventions, and overall patient outcome) were compiled into a table and a brief description of each article was written. This evidence table is available at http://www.aapcc.org/DiscGuidelines/valproic%20acid%20evidence%20table%202006-6-8.pdf.

The table of all abstracted articles was then forwarded to the panel members for review and consideration in developing the guideline. Every attempt was made to locate foreign language articles and have their crucial information extracted, translated, and tabulated. A written summary of the data was created and distributed by the abstractor. Copies of all of the abstracted articles were made available for reading by the panel members on a secure American Association of Poison Control Centers (AAPCC) website.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

An expert consensus panel was established to develop the guideline (see Appendix 1 of the original guideline document). The American Association of Poison Control Centers (AAPCC), the American Academy of Clinical Toxicology (AACT), and the American College of Medical Toxicology (ACMT) appointed members of their organizations to serve as panel members. To serve on the expert consensus panel, an individual had to have an exceptional record in clinical care and scientific research in toxicology, board certification as a clinical or medical toxicologist, significant US poison control center experience, and be an opinion leader with broad esteem. Two specialists in poison information were

included as full panel members to provide the viewpoint of the end-users of the guideline.

Guideline Writing and Review

A guideline draft was prepared by the lead author. The draft was submitted to the expert consensus panel for comment. Using a modified Delphi process, comments from the expert consensus panel members were collected, anonymously copied into a table of comments, and submitted to the lead author for response. The lead author responded to each comment in the table and, when appropriate, the guideline draft was modified to incorporate changes suggested by the panel. The revised guideline draft was again reviewed by the panel and, if there was no strong objection by any panelist to any of the changes made by the lead author, the draft was prepared for the external review process.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The rating scheme for the strength of the recommendation (A-D, Z) is directly tied to the level of evidence supporting the recommendation.

Grade of Recommendation	Level of Evidence
A	1a
	1b
	1c
B	2a
	2b
	2c
	3a
	3b
C	4
D	5
Z	6

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External review of the second draft was conducted by distributing it electronically to American Association of Poison Control Centers (AAPCC), American Academy of Clinical Toxicology (AACT), and American College of Medical Toxicology (ACMT) members and the secondary review panel. The secondary review panel consisted

of representatives from the federal government, public health, emergency services, pediatrics, pharmacy practice, and consumer organizations (see Appendix 3 in the original guideline document). Comments were submitted via a discussion thread on the AAPCC web site or privately through email communication to AAPCC staff. All submitted comments were stripped of any information that would identify their sources, copied into a table of comments, and reviewed by the expert consensus panel and the lead author. The lead author responded to each comment in the table and his responses and subsequent changes in the guideline were reviewed and accepted by the panel.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Grades of recommendation (A-D, Z) and levels of evidence (1a-6) are defined at the end of the "Major Recommendations" field.

1. All patients with suicidal intent, intentional abuse, or in whom a malicious intent is suspected (e.g., child abuse or neglect) should be referred to an emergency department **(Grade D)**.
2. Patients who are symptomatic (more than somnolence or exhibiting coma or seizures) after a valproic acid ingestion should be referred to an emergency department **(Grade C)**.
3. Asymptomatic patients with an unintentional acute ingestion of 50 mg/kg or more or asymptomatic patients who are taking the drug therapeutically and who take an additional single acute ingestion of 50 mg/kg or more of any valproic acid formulation should be referred to an emergency department for evaluation **(Grade C)**.
4. Patients with unintentional ingestions of immediate-release valproic acid formulations, who are asymptomatic, and more than 6 hours has elapsed since the time of ingestion, can be observed at home **(Grade C)**.
5. Patients with unintentional ingestions of delayed-release or extended-release formulations of valproic acid who are asymptomatic, and more than 12 hours has elapsed since the time of ingestion, can be observed at home **(Grade C)**.
6. Pregnant women who ingest below the dose for emergency department referral and do not have other referral conditions should be directed to their primary care obstetrical provider for evaluation of potential maternal and fetal risk. Routine referral to an emergency department for immediate care is not required **(Grade D)**.
7. Do not induce emesis **(Grade C)**.
8. Activated charcoal can be administered to asymptomatic patients who have ingested valproic acid within the preceding hour **(Grade C)**. Prehospital activated charcoal administration, if available, should only be carried out by health professionals and only if no contraindications are present. Poison centers should follow local protocols and experience with its use. Do not delay transportation in order to administer activated charcoal **(Grades D)**.
9. In patients who have ingested valproic acid and who are comatose, naloxone can be considered for prehospital administration in the doses used for treatment of opioid overdose, particularly if the patient has respiratory depression **(Grade C)**.
10. A benzodiazepine can be administered by emergency medical services (EMS) personnel if convulsions are present and if authorized by EMS medical

direction, expressed by written treatment protocol or policy, or if there is direct medical oversight **(Grade C)**.

Definitions:

Grades of Recommendation and Levels of Evidence

Grade of Recommendation	Level of Evidence	Description of Study Design
A	1a	Systematic review (with homogeneity) of randomized clinical trials
	1b	Individual randomized clinical trials (with narrow confidence interval)
	1c	All or none (all patients died before the drug became available, but some now survive on it; or when some patients died before the drug became available, but none now die on it.)
B	2a	Systematic review (with homogeneity) of cohort studies
	2b	Individual cohort study (including low quality randomized clinical trial)
	2c	"Outcomes" research
	3a	Systemic review (with homogeneity) of case-control studies
	3b	Individual case-control study
C	4	Case series, single case reports (and poor quality cohort and case control studies)
D	5	Expert opinion without explicit critical appraisal or based on physiology or bench research
Z	6	Abstracts

CLINICAL ALGORITHM(S)

An algorithm is provided in Appendix 4 of the original guideline document for triage for acute and single acute-on-chronic valproic acid poisoning.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate out-of-hospital triage and initial out-of-hospital management of patients with suspected valproic acid poisoning

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline has been developed for the conditions prevalent in the United States. While the toxicity of valproic acid is not expected to vary in a clinically significant manner in other nations, the out-of-hospital conditions could be much different. This guideline should not be extrapolated to other settings unless it has been determined that the conditions assumed in this guideline are present.
- This guideline is based on an assessment of current scientific and clinical information. The expert consensus panel recognizes that specific patient care decisions might be at variance with this guideline and are the prerogative of the patient and the health professionals providing care, considering all of the circumstances involved. This guideline does not substitute for clinical judgment.

Limitations of the Literature

Unfortunately, the data on acute valproic acid poisoning generally suffered from a number of limitations: 1) much of the data was determined by retrospective observations and based on estimates of dose provided by patients or family members, raising questions about the accuracy of the dose estimates; 2) the dose-effect information was confounded in many cases by the presence of co-ingestants, differences in treatment measures provided, and concurrent medical conditions that could have altered the clinical presentation or outcome; 3) as there are several formulations of valproic acid and divalproex products, many authors failed to report exactly which product was involved; 4) among larger case series, many of the patients remained asymptomatic, and product formulations, ingestion doses, and frequency and severity of effects were typically reported as ranges of values, percentages, or means, so individual doses resulting in specific effects could not be determined; and 5) among the few prospective trials available, valproic acid was administered in therapeutic doses, which would be expected to be much smaller than doses likely to be seen in an overdose or poisoning.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Manoguerra AS, Erdman AR, Woolf AD, Chyka PA, Caravati EM, Scharman EJ, Booze LL, Christianson G, Nelson LS, Cobaugh DJ, Troutman WG. Valproic acid poisoning: an evidence-based consensus guideline for out-of hospital management. Washington (DC): American Association of Poison Control Centers; 2006. 23 p. [85 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Dec 22

GUIDELINE DEVELOPER(S)

American Association of Poison Control Centers - Professional Association

SOURCE(S) OF FUNDING

Health Resources and Services Administration, U.S. Department of Health and Human Services

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Booze's husband is employed by AstraZeneca.

Dr. Erdman was employed by AstraZeneca at the time of his work on this guideline.

There are no other potential conflicts of interest reported by the expert consensus panel or project staff regarding this guideline.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Poison Control Centers.

Print copies: Available from the American Association of Poison Control Centers, 3201 New Mexico Avenue NW, Suite 330, Washington, DC 20016

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on December 18, 2007. The information was verified by the guideline developer on January 14, 2008.

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